

55. Fab fragments which bind specifically to a venom of a snake of the Crotalidae family, and which are essentially free from contaminating Fc as determined by immunoelectrophoresis using an anti-Fc antibody.

56. The Fab fragments of claim 55, wherein an antibody source for said Fab fragments is IgG(T).

57. The Fab fragments of claim 55, wherein an antibody source for said Fab fragments is polyvalent IgG(T).

58. The Fab fragments of claim 55, wherein said Fab fragments are derived from IgG(T).

59. The Fab fragments of claim 55, wherein said Fab fragments are derived from polyvalent IgG(T).

60. The Fab fragments of any one of claims 40, 45, 50, and 55, wherein said detection by immunoelectrophoresis further comprises a specific Fc immunoassay.--

REMARKS

Applicants have proposed amending the specification to update the status of the parent U.S. patent application referred to in the specification. Applicants have also proposed amending claims 40 to 49 and the title to recite "Fab" instead of "F(ab)" and "antivenom" instead of "antivenin." This Amendment is supported throughout the specification and the original claims. Applicants have also proposed adding new claims 50-60.

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FINNEGAN, HENDERSON,
FARABOW, GARRETT
& DUNNER, L.L.P.
1300 I STREET, N.W.
WASHINGTON, DC 20005
202-408-4000

New Claims 50-60

New claims 50-59 are identical to claims 40-49 except that they recite "the Crotalidae family" rather than "the Crotalus genus." Applicants respectfully submit that new claims 50-60 are fully supported by the specification and original claims.

New claims 50-60 comply with the written description requirement when "the originally filed application would have conveyed to a person of ordinary skill in the art that applicants invented the subject matter latter claimed by them." Staechelin v. Secher, 24 U.S.P.Q.2d 1513 (Bd. Pat. App. & Int. 1992). Applicants respectfully submit that the specification would have conveyed to a person of ordinary skill in the art that Applicants invented the subject matter of new claims 50-60, which recite "the Crotalidae family."

Rattlesnakes are members of two genera: The Crotalidae family is one of five families of venomous snakes. Russell, F.E., Snake Venom Poisoning, Ch. 1, page 5 (copy enclosed). Members of the Crotalidae family are commonly called crotalids or pit vipers and include the genus *Crotalus*. Id. at 6.

Applicants' specification concerns snake venoms. Specification at page 4, lines 6-11. Applicants' examples use venom from four members of the Crotalidae family. Specification at page 13, lines 16-20. Furthermore, Applicants compared their antivenom with Wyeth's commercial Antivenin (**Crotalidae**) Polyvalent (ACP). Specification at page 15, lines 28.35. As is suggested by its name, this product is used for the treatment of most pit viper bites. Dorland's Illustrated Medical Dictionary, 95 (26th, 1981) (copy enclosed). Finally, Applicants' original antivenin composition claims

were not limited to the *Crotalus* genus. Accordingly, one of ordinary skill in the art would have known that Applicants invented the subject matter of new claims 50-60.

New claims 50-60 are also enabled. When Applicants compared the Fab fragment of the invention with those obtained from the Wyeth Antivenin (**Crotalidae**) ACP by precipitation, which are used to treat Crotalidae envenomation, they found that the fragments "appear to be the same." Specification at page 23, lines 9-13.

Accordingly, Applicants respectfully request entry of new claims 50-60.

**Rejection of claims 40-49
under 35 U.S.C. § 103 (Item 18)**

The Examiner rejected claims 40-49 under 35 U.S.C. § 103 as allegedly being unpatentable over Sullivan et al. in view of Coulter et al. and Smith et al., as evidenced by Stedman's Medical Dictionary. Specifically, the Examiner contends that it would have been obvious to one of ordinary skill in the art to utilize Sullivan et al.'s purified antivenom polyvalent antibodies against venom of the *Crotalus* genus to produce antivenom compositions consisting of Fab fragments.¹ The Examiner asserts that one of ordinary skill in the art would have been motivated to combine these references because Coulter et al. teaches a method of producing antivenom Fab fragments, and Smith et al. teaches the advantages of Fab fragments for the neutralization and clearance of toxic substances in therapeutic applications. Paper No. 21 at paragraph bridging pages 3 and 4.

¹ As discussed above, Applicants note that new claims 50-60 recite "the Crotalidae family," rather than "the *Crotalus* genus." Applicants submit that their remarks concerning this rejection also apply to any possible rejection of claims 50-60.

Applicants respectfully traverse this rejection. The Examiner concedes that the primary reference, Sullivan et al., does not teach a Fab containing antivenom. Id. at page 3, lines 12-13. The Examiner asserts that Coulter et al. provides this teaching because Coulter et al. teaches a composition of Fab fragments against textilotoxin, and Stedman's Medical Dictionary defines antivenom as "an antitoxin specific for an animal or insect toxin." Id. at page 3, lines 14-19. Thus, the Examiner concludes that Coulter et al. teaches antivenom Fab fragments. Id. at page 3, lines 19-20.

The Examiner contends that Stedman's Medical Dictionary defines antivenom as "an antitoxin specific for an animal or insect toxin." Paper No. 21 at page 3, lines 17-19 (emphasis added). However, Stedman's Medical Dictionary actually defines antivenom as "an antitoxin specific for an animal or insect venom." Stedman's Medical Dictionary at page 94. As shown by the enclosed definition, snake venom comprises many different toxins. Dorland's Illustrated Medical Dictionary, 1449 (26th ed. 1981). Crotalid Snake Venoms comprises 20 different compounds. Russell at Ch. 6, page 168 (copy enclosed). Overall, Crotalid snake venoms comprise over 100 different synergistic compounds, many of which have major physiologic and pharmacologic properties, including proteolytic enzymes, collagenases, hyaluronidases, phospholipases A, B, and C, pre- and post-synaptic neurotoxins, procoagulants, anticoagulants, and other simple to complex peptides with molecular weights ranging from less than 1 to more than 100,000 daltons. Since Coulter et al. teaches a composition of Fab fragments against textilotoxin, a single snake toxin, Coulter et al. does not teach an antivenom.

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FARABOW, GARRETT
& DUNNER, L.L.P.
1300 I STREET, N.W.
WASHINGTON, DC 20005
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To further clarify Applicants' claimed invention, Applicants have amended claims 40 and 45 to specify that the venom comprises more than one toxin.

Accordingly, Applicants request withdrawal of this rejection.

Not only was there no suggestion to combine the references as the Examiner has suggested, prior to Applicants' invention, there was no reasonable expectation of success. Cleavage of an IgG molecule with papain results in separate Fab fragments and an Fc fragment. In contrast, cleavage with pepsin results in a single Fab'₂ fragment and a smaller Fc fragment. A single Fab'₂ fragment comprises the two Fab fragments as well as the portion of the heavy chains connected by a disulfide bond. Thus, each Fab has its own, single antigen binding site, and the Fab'₂ fragment has two antigen binding sites.

Since the Fab'₂ fragment contains two antigen binding sites, it may precipitate the antigen it binds. Stewart Sell, Basic Immunological: Immune Mechanism in Health and Disease 89, Fig. 6-3 (1987) (copy enclosed). In contrast, although an Fab fragment can bind an antigen, it cannot precipitate the antigen because it has only one antigen binding site. Id. Furthermore, a Fab-venom protein complex has a molecular weight that is greater than the molecular weight filtration limit of the kidney--typically 60 kd. Sullivan Declaration at sentence bridging pages 3 and 4. Therefore, Fab would not precipitate the venom protein, and the Fab-venom protein complex would remain in solution.

Fab also has a much shorter half-life than venom protein. Indeed, Fab fragments require only 24 to 26 hours to be totally eliminated, whereas venom proteins

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& DUNNER, L. L. P.
1300 I STREET, N. W.
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require weeks for elimination. Sullivan Declaration at page 3, lines 24-26. For example, Ownby et al., Southern Medical Journal (August 10, 1996) (copy enclosed), detected Crotalidae snake venom in a patient forty-six days after envenomation.

Fab's inability to precipitate venom proteins and its short half-life led those of ordinary skill in the art to believe that Fab would not be effective in treating venom. Indeed, those of ordinary skill in the art actually believed that Fab would be harmful. Although Fab might bind venom proteins quickly, the Fab cannot precipitate the venom proteins. Therefore, the Fab-venom protein complex would remain in solution. Since Fab has a large volume of distribution, those of ordinary skill in the art believed that the Fab might actually introduce the venom proteins into other areas of the body than they were originally located.

Since Fab has a much shorter elimination period than venom proteins, and since free Fab was eliminated more quickly than venom protein, the bound Fab would unbind from the venom proteins to equilibrate. Thus, those of ordinary skilled in the art believed that Fab would introduce venom proteins into areas of the body where they would not otherwise be located and would prolong the presence of the venom proteins in the body. Sullivan Declaration at page 5, last paragraph, through page 6, second paragraph.

Accordingly, prior to Applicants' invention, not only had no one successfully used an antivenom comprising Fab fragments, no one had even tried such an Fab composition. This is despite the fact that antivenoms comprising intact antibodies have been available since at least 1947, and antivenoms comprising Fab₂ fragments have

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FARABOW, GARRETT
& DUNNER, L. L. P.
1300 I STREET, N. W.
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been available since at least 1969. Smith Declaration at page 2, third full paragraph. Although those of ordinary skill in the art not only used intact immunoglobulins in antivenom compositions, but also digested these intact immunoglobulins to yield Fab₂ fragments, they went no further because of the expected disadvantages of Fab fragments.

Indeed, one of ordinary skill in the art cited these very concerns for antitoxin Fab therapy. Balthasar et al. studied the effect of antidigoxin Fab fragments for minimizing drug toxicity. Antidigoxin Fab fragments are the very fragments utilized by Smith et al., the reference the Examiner relies upon as allegedly providing the motivation to combine the cited references.

Balthasar et al. conclude, "there are, however, several concerns which must be addressed before the implementation of this type of therapy. First, the alteration of drug distribution which accompanies antibody drug complexation may result in a **potentiation of drug toxicities** or the development of **new drug toxicities** in certain cases The risk of **redistributing systemic toxicity**, rather than minimizing systemic toxicity, should be appreciated as a potential outcome of the proposed approach." Balthasar et al. at page 738, paragraph bridging cols. 1 and 2 (emphasis added).

The Examiner dismisses Balthasar et al. on the ground that Balthasar et al. referred to alpha-amatoxin. Paper No. 21 at page 5, last full sentence. However, as Applicants have noted above, Balthasar et al. concerns digoxin, the same toxin as utilized by Smith et al., the reference the Examiner relies upon as allegedly suggesting

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combining these cited references. Furthermore, although Balthasar et al. cite Faulstich et al., which concerns alpha-amatoxin, Balthasar et al. discuss this reference in the context of drug-binding Fab fragments for the treatment of drug toxicity. Thus, Balthasar et al. believed that the results and teachings of Faulstich et al. were relevant and generalizable to general drug toxicity.

The Examiner dismisses the Smith and Sullivan Declarations on the ground that they allegedly ignore that Coulter et al. teach that Fab antivenom can neutralize snake venom toxin. Id. at page 7, lines 8-10. Applicants respectfully disagree with this characterization. The Smith Declaration contains results showing that Fab antivenom was as effective as Fab₂ antivenom at a much lower dosage. Smith Declaration at page 5. In contrast, Coulter et al. teach a 20 to 30 percent loss of activities for Fab fragments. Thus, the results presented in the Smith Declaration show the unexpected results of the present invention, which are superior to Coulter et al.'s results.

The Examiner also dismisses the Smith and Sullivan Declarations on the basis of teachings contained in Sullivan (1986). However, the present application is entitled to a filing date of October 9, 1984. Thus, Sullivan (1986) is not available as prior art to establish a reasonable expectation of success.

The Examiner dismisses Applicants' evidence of long felt but unmet need, as exemplified by the FDA's designation of the first purified Fab antivenom as an orphan drug, on the ground that orphan drug is an ovine Fab. Paper No. 21 at page 7, lines 24-27. However, Smith et al., the reference the Examiner relies upon as providing the suggestion to combine the cited references, also involves an ovine preparation.

Furthermore, Sorkine et al. state that there was no difference in the efficacy of ovine and equine Fab antivenom. Sorkine et al. at abstract.

Applicants respectfully submit that the Examiner cannot rely upon Smith et al., which used an ovine preparation, while rejecting Applicants' evidence of long felt but unmet need based upon another ovine preparation. If the Examiner persists in dismissing this evidence on this ground, Applicants respectfully request the Examiner to explain why Smith et al.'s ovine data is relevant, but Applicants' ovine data is not.

Finally, the Examiner dismisses the clinical results in the Smith Declaration on the grounds that the specification does not utilize the specific Fab antivenom composition utilized in that clinical study. Id. at sentence bridging pages 7 and 8. Although the data in the Smith Declaration concerned an Fab antivenom composition directed to the venom of a species of a different genus of snake, these data are relevant to the present invention, especially new claims 50-60, which recite a snake of the Crotalidae family. This Fab composition is obtained in the same way as Applicants' composition and is directed at the same goal, neutralizing snake venom toxins. If the Examiner continues to maintain that these data are not relevant to Applicants' invention, Applicants respectfully request that the Examiner provide reasons or evidence to support his assertion.

**Rejection of claims 43, 44, 48, and 49 under
35 U.S.C. § 112, s cond paragraph (Item 20)**

The Examiner rejected claims 43, 44, 48, and 49 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicants regard as their invention. Specifically, the Examiner contends that the claims reciting polyvalent IgG(T) are duplicative of the claims reciting simply IgG(T).

Applicants respectfully traverse this rejection. The Examiner supports the assertion that these claims are duplicative by stating that "both claims read on the same product." Applicants respectfully submit that this is not a valid test for duplicative claims. Indeed, claims reading on the same product are common in the same patent. For instance, many patents have genus and species claims. By definition, both the genus and the species claims would read upon the species. Thus, Applicants respectfully request withdrawal of this rejection.

**Rejection of claims 45-49
under 35 U.S.C. § 103 (Item 21)**

The Examiner rejected claims 45-49 under 35 U.S.C. § 103 as allegedly being unpatentable over Sullivan et al. in view of Coulter et al. Specifically, the Examiner contends that Sullivan et al. teach antivenom polyvalent antibodies and that Coulter et al. teaches a method for producing Fab fragments against textilotoxin. Paper No. 21 at page 8, lines 21, through page 9, line 20. The Examiner contends that Coulter et al. suggest combining these two references because they teach that "EIAs of higher

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FINNEGAN, HENDERSON,
FARABOW, GARRETT
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
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sensitivity have been claimed when Fab enzyme is used instead of IgG enzyme."

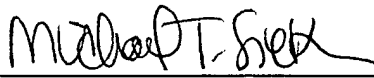
Paper No. 21 at page 9, lines 21-27.

Applicants respectfully traverse this rejection. As Applicants discussed in the previous obviousness rejection, Coulter et al. teach Fabs against a single neurotoxin, not against a complex mixture of enzymes and other peptides, like venom. Thus, the alleged suggestion of Coulter et al. to use Fabs, instead of whole IgG, would apply solely to individual toxins. Accordingly, there is no suggestion to prepare Fabs to a venom of a species of the Crotalus genus, and Applicants respectfully request withdrawal of this rejection.

If there are any fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 60-0916. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested, and the fee should also be charged to our Deposit Account.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

By: 

Michael T. Siekman
Reg. No. 36,276

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